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REC'D 21 OCT 2004
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ZRC-NIPR-008	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IN 03/00241	International filing date *(day/month/year)* 15.07.2003	Priority date *(day/month/year)* 16.07.2002
International Patent Classification (IPC) or both national classification and IPC C07D417/12		
Applicant CADILA HEALTHCARE LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.02.2004	20.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Baston, E Telephone No. +49 89 2399-8229

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 03/00241

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-59 as originally filed

Claims, Numbers

1-22 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 21,22 "with respect to industrial applicability"

   because:

   ☒ the said international application, or the said claims Nos. 21,22 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 8 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18,20-22
	No:	Claims	19
Inventive step (IS)	Yes:	Claims	1-18,20-22
	No:	Claims	19
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

   see separate sheet

To section III

Claims 21 and 22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

To section V

The following documents were cited in the search report and were considered for the examination of the present application:

D1: Sohda, T. et al. ; D2: Momose, Y. et al.; D3: EP 0 193 256; D4: EP 0 008 203
D5: EP 0 257 781; D6: WO 02 088120; D7: WO 93 22445

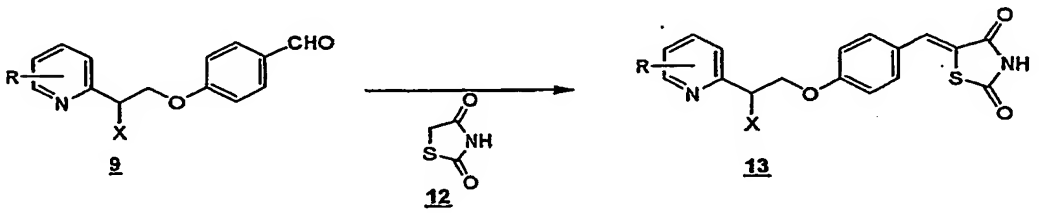
The present application relates to processes for the preparation of intermediates for the production of Pioglitazone and derivatives thereof. Furthermore the application deals with a process for the production of a hydrochloride salt, pharmaceutical compositions and methods.

Claims 1-6 relate to processes which include the transformation to the target molecule 1, whereas claims 9-12,14-15 and 17-18 are directed to other intermediates. These claims are novel since no document of the prior art anticipates these processes (Art. 33(2) PCT).
Claims 7,8, 13 and 16 (compounds) are novel due to the exact definition of the group X which excludes an anticipation from D1 (scheme 2).
The conversion of e.g. Pioglitazone to its hydrochloride salt (and pharmaceutical compositions) are known from e.g. D1 (compare page 41). Thus claim 18 can be considered novel in view of the fact that it incorporates the process of claim 1.
Claim 19 is not novel. It has to be stated that a preparation procedure cannot be considered to limit the scope of protection. Product by process claims are only allowable if no other possibilty is given to determine a chemical entity.
Claims 20-22 are novel, since no document of the prior art anticipates these compounds and related methods. However it has to be questioned how a pharmaceutical composition can be derived from possibly toxic intermediate compounds (13 and 14, e.g. Mesylates, Tosylates).

Claims 1-18 and 20-22 are considered to be inventive (Art. 33(3) PCT) for the following reason:
The claimed process relates to the preparation of various compounds according to formula (1) and to intermediates. Based on the arguments of the Applicant and in view of the prior art it is assumed that the presently claimed process represents an improvement due to e.g. a lower by-product formation.
However the scope of claim 1 also extends to those congeners which cannot be direct precursors for compound 1 (X=OH) thus arising a lack of clarity and a lack of support from the description (Art. 6 PCT).

For the assessment of the present claims 21 and 22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

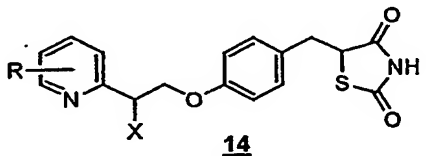
selected from ammonia, methyl amine, ethyl amine, *n*-butyl amine, pyrrolidine, piperidine, pyridine, morpholine, piperazine, diethylamine, di-isopropyl amine or triethyl amine and catalytic amount of organic acid selected from acetic acid, *p*-tolune sulfonic acid, hydrochloric acid, or hydrobromic acid to obtain compound of formula **13**.



ii) chemoselective reduction of the compound of formula **13**, as claimed in any preceding claims above to obtain **14**.

iii) Reduction of compound of formula **14** as claimed in claim 1 to obtain the compound of formula **1**.

7. A compound of formula **14**, or its salts, where X represents Cl, Br, OMs, and OTs and R represents straight chain or branched alkyl group of one to six carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, pentyl, *iso*-pentyl, neo-pentyl, hexyl, preferably lower alkyl groups of one to three carbon atoms.



8. A compound as claimed in claim 7 wherein R represents 5-ethyl;

9. A process for the preparation of compounds of formula **14**, where X represents OH, Cl, Br, OMs, and OTs & R represents straight chain or branched alkyl group of one to